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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/000,297	12/04/2001	Shu Wang	11042-003	8915

7590 06/03/2004

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EXAMINER	
ROBERTS, PAUL A	

ART UNIT	PAPER NUMBER
3731	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/000,297	WANG ET AL.	
	Examiner	Art Unit	
	Paul A Roberts	3731	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38 and 40-133* is/are pending in the application.

4a) Of the above claim(s) *1-21,23 and 58-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24-38,40-57 and 98-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 131 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no support in the specification for placing 100 ug of protein into a 10mm conduit. Applicant likely meant 100 um of protein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 22, 24-26, 27-31, 40, 42, 45-49, 51, 54, 55, and 56 are rejected under 35 U.S.C. 103(a) as being obvious over Peulve et al. (Peulve) 2002/0071828 in view of patent 5,256,765 issued to Leong, Kam W (Leong).

Regarding claim 22, Peulve discloses making a nerve guide polymer in the shape of a tube. Peulve in [0018] discloses that a gene delivery system can be incorporated into the nerve guide. Puelve lists materials one could use to assemble the guide but doesn't disclose polyphosphoester in the list of materials. Leong '765 teaches a polyphosphoester material that is

intended to be used as a material for a prosthesis. The Leong material has additional advantages such as it is biodegradable and can act as a therapeutic agent delivery device. Additionally Leong does mention this particular material is especially useful in genetic engineering. At the time of the invention it would have been obvious to one having ordinary skill in the art to substitute the Leong material for nerve guides into the Peulve nerve guide system since the Leong material is biodegradable and useful for delivery of therapeutic agents.

Regarding claims 24-26, Leong discloses that the molecular weight of the polyphoester can be any weight from 2000- 10^6 daltons.

Regarding claims 27-29, the combined Peulve device discloses all of claim 22, but doesn't disclose the porosity of the material. However, it is well known in the art to vary the porosity of a material to change the amount of time the material takes to dissolve invitro. At the time of the invention it would have been obvious to one having ordinary skill in the art to make the porosity 8% or 35% to modify the amount of time the material requires for complete dissolution.

Regarding claims 30 and 31, the combined Peulve device discloses a nerve with a 1.5 mm diameter.

Regarding claim 40, the Peulve-Leong device discloses ('828 [0041]) the use of a complex of DNA and a cationic polymer or lipid loaded into a cuff.

Regarding claim 42, the Peulve-Leong device discloses the incorporation of polyethylenimine into the cationic polymer [0041].

Regarding claim 45, the Peulve-Leong device doesn't specifically disclose that the gene encodes a neurotrophic protein. The combined device has a genetic delivery system designed to

deliver DNA to a neuron. Neurons are comprised of proteins. Thus the type of protein the Peulve-Leong DNA encodes must be neurotrophic proteins since the DNA is being delivered to a neuotrophic site.

Regarding claims 46 and 56, the Peulve-Leong device discloses that BDNF ('828 [024]) is a preferred neutrophin to use in the gene delivery system of Peulve.

Regarding claim 47, the Peulve system is designed as a drug delivery system.

Regarding claims 48 and 49, the protein delivery system comprises microspheres that contain protein wherein said protein will be inherently released from the microspheres progressively. The microspheres are made from a poly(phosphoester) polymer.

Regarding claim 51, the nerve guide can be alternatively made from poly(lactic-co-glycolic acid) (disclosed in Leong).

Regarding claim 54, Leong discloses the nerve conduit should release protein from the microspheres, but does not disclose for what temporal duration the microspheres should release the protein. Providing the nerve cells with a long, constant source of protein will improve the regenerative qualities of the procedure. At the time of the invention it would have been obvious to one having ordinary skill in the art to modify the Peulve-Leong device so that microspheres will dissolve very slowly thus releasing the protein for three months or longer, and thereby improving the regenerative qualities of the procedure. Also, methods of modifying the microspheres' longevity are well known in the art. Increasing porosity or surface area of the sphere will result in faster dissolution times.

Regarding claim 55, the Peulve-Leong device doesn't disclose the length of protein to be loaded per length of conduit. It would have been an obvious matter of design choice to modify

the Peulve-Leong device to have the 10 microns of protein to be loaded per 10 mm of conduit since the applicant has not disclosed this loading procedure would solve any stated problem or is for any particular purpose and it appears that the undisclosed amount of protein added by Peulve would perform equally well.

2. Claims 32-38 are rejected under U.S.C. 103(a) as being obvious over the combined Peulve device of claim 22, in further in view of Li 5026381.

Regarding claims 32-33, the combined Peulve device discloses a nerve guide. Neither Peulve nor Leong disclose the wall thickness of the nerve guide, but nerve guide conduits typically have a wall thickness of about 0.3mm (which includes thicknesses from .21 mm to .39mm). Li 5026381 teaches the thickness of nerve guides, "Typically for a 1mm x .5cm conduit having an overall wall thickness of about .3mm..." At the time of the invention it would have been obvious to one having ordinary skill in the art to make the wall thickness of the Leong device about .3 mm because Li teaches this size is the typical size of a nerve guide.

Regarding claims 34-37, the combined Peulve device discloses a device with many layers of material (figure 1 of Li shows a multi-layered material). The Puelve device inherently has a multilayered wall. A collagen wall for a nerve guide appears as shown as Li. The thickness of the individual layers is not disclosed. It would have been an obvious matter of design choice to modify the Leong-Li device to have a wall layer thickness of 25 micrometers since the applicant has not disclosed the layer thickness of 25 micrometers would solve any stated problem or is for any particular purpose and it appears that the undisclosed layer thickness of Li would perform equally well.

Regarding claim 38, the combined Peulve device discloses all the limitations of claim 22. Peulve does not disclose that the outer surface of the wall has a greater microporosity than the luminal surface of the conduit. Li '381 teaches making a conduit with an outer layer that is more porous than the inner layer and provides motivation to apply this technique on other nerve guides (see column 4, last paragraph.) Li designs the nerve guide to have this configuration to instill mechanical strength to the guide, while maintaining the benefits of a highly porous material. At the time of the invention it would have been obvious to one having ordinary skill in the art to modify the Peulve-Leong device to have an outer surface of the wall that has a greater microporosity than the luminal surface of the conduit to instill mechanical strength to the guide, while maintaining the benefits of a highly porous material.

3. Claim 41 is rejected under 35 U.S.C. 103(a) as being obvious over in Peulve et al. 2002/0071828 in view of Leong '092, in further view of Davis et al. 2002/0044972. Regarding claim 41 the Peulve-Leong device discloses the nerve guide contains DNA particles but doesn't disclose the size of the complex's particles. The applicant has not disclosed any criticality for the size of the particles. It would have been an obvious matter of design choice to modify the Peulve device to have a DNA particle size of 20nm since the applicant has not disclosed the size of the particles would solve any stated problem or is for any particular purpose and it appears that the DNA particles of Peulve and Leong would perform equally well. Additionally, Davis et al. 2002/0044972 teaches a method and motivation to reduce DNA particle size into a range of 1000nm to 10nm, to enable DNA to more easily enter the target cells. At the time of the invention it would have been obvious to one having ordinary skill in the art to reduce the DNA

particles of the combined Peulve device to 20nm to enable the DNA to more easily enter the target cells as taught by Davis et al.

4. Claims 43 and 44 are rejected under 35 U.S.C. 103(a) as being obvious over Peulve et al. 2002/0071828 in view of Leong '092, in further view of Neuman et al 2003/0027779.

Regarding claim 43, the Peulve-Leong device discloses all of claim 40, but does not disclose the incorporation of phosphatidylethanolamine, but this compound is a well known gene delivery agent. Neuman et al '779 discloses the method of injecting DNA directly into a nerve cell using said compound as the delivery agent. At the time of the invention it would have been obvious to one having ordinary skill in the art to use phosphatidylethanolamine as the drug delivery agent for the Puelve-Leong conduit because Neuman teaches this agent can be used to transmit DNA into nerve cells.

Regarding claim 44, the Peulve-Leong device discloses all the limitations of claim 43, but doesn't disclose the incorporation of GenPORTER™, but this compound is a well-known gene delivery agent. GenePORTER™ is a commercial product designed to transfer DNA to a cell. At the time of the invention it would have been obvious to one having ordinary skill in the art to use a commercial gene delivery product to delivery genetic information.

5. Claim 50 is rejected under 35 U.S.C. 103(a) as being obvious over in Peulve et al. 2002/0071828 in view of Leong '092, in further view of Mao et al. 6485737. Regarding claim 50, the Peulve-Leong device doesn't disclose which subunit the conduit contains, but the claimed subunit is obvious to use because it is biodegradable (bioabsorbable). Mao teaches the use of the

claimed subunit and incorporates its use in a bioabsorbable polymeric implant. Mao (col. 1, lines 20-30) explains using the claimed subunit is beneficial because bioabsorbable compounds obviate the need to invasively remove the device. At the time of the invention it would have been obvious to one having ordinary skill in the art to use the Mao subunit in the Peulve-Leong conduit to provide the Leong conduit with bioabsorbable qualities.

6. Claims 52 & 53 are rejected under U.S.C. 103(a) as being obvious over the combined Peulve device of claim 22, in further in view of Schwendeman et al. US 20020009493. The combined Peulve device discloses the use of microspheres in a protein delivery system but does not suggest the size of microspheres. The applicant has not disclosed any criticality for the size of the microspheres. It would have been an obvious matter of design choice to modify the Peulve device to have a microsphere size of 10um since the applicant has not disclosed the size of the particles would solve any stated problem or is for any particular purpose and it appears that the microspheres of Peulve and Leong would perform equally well. Additionally, Schwendeman et al '493 teaches a method and motivation to use microspheres for protein delivery with a 10um to 100um size. The purpose of using very small particles is to help insure continuous, gradual release of protein into the target cells. At the time of the invention it would have been obvious to one having ordinary skill in the art to modify the combined Peulve device to use microspheres of about 10um to enable the microspheres to gradually release protein into the target cells.

7. Claim 57 is rejected under 35 U.S.C. 103(a) as being obvious over Peulve et al. 2002/0071828 in view of Leong '092, in further view of Stone 5258043. Regarding claim 57, the Peulve-Leong device discloses a polyphoester nerve guide, but doesn't disclose the conduit should contain Schwann cells. Stone 5258043 teaches a nerve guide should be seeded with Schwann cells to help promote further tissue regrowth (column 2, lines 10-30). At the time of the invention it would have been obvious to one having ordinary skill in the art to seed the nerve guide of Leong device with Schwann cells, because Stone teaches doing so will result in greater nerve regrowth.

8. Regarding claims 98-133, these claims repeat the same claimed subject matter as presented above. These claims are rejected for the same reasons as their corresponding claims above. For example, claim 98 is rejected for the same reason claim 38 was. That is for claim 98, for example, Peulve in view of Leong, in further view of Li, render obvious the limitations of claim 98.

Response to Arguments

Applicant's arguments filed 1/9/04 have been fully considered but they are not persuasive. The applicant has claimed priority of the one of references used in the rejection. Thus a new grounds for rejection is necessary in response to this amendment. The applicant's arguments with respect to the old combination of Leong in view Peulve are answered when the arguments are not moot.

Regarding claims 27-29, "the examiner provided no basis in the prior art for adjusting the surface porosity..." The examiner previously stated clearly that is well known in the art to adjust surface porosity to modify dissolution time. Varying porosity for corporal implants is a known practice. Raising porosity promotes tissue ingrowth and decreases dissolution time for drug delivery compounds (such as hydrogels), while lowering porosity increases structural rigidity, decreases implant failure, and lengthens dissolution time for drug delivery compounds. As described above, the combination Peulve device teaches the basic device of claim 22. Selecting a specific porosity or range of porosity to construct the Peulve device demonstrates only routine skill in the art. There does not appear to be any critical reason why the applicant selected 8% or 35% as the surface porosity, and given the intended use of the combined Peulve device, one of ordinary skill in the art would select such a porosity based on the intended use of the Peulve device. See Kuhn US 3916905 which teaches these known scientific principles.

Regarding claim 38, the applicant's arguments are considered, but the passage quoted and explained does not provide a discrete function or purpose for a decreasing wall porosity from the inside to the outside wall. Without any type description or disclosure as to why the applicant is making the outer layer more porous than the inner layer, it can be argued that the reason is simply ornamental, which is not a patentable difference. Assuming that the function of the feature **is** disclosed, even though the examiner has read the disclosure, and examiner asserts that said function is not disclosed, this feature would still not be unobvious over the prior art. The applicant should note that Li '381 teaches making a conduit with an outer layer that is more porous than the inner layer and provides motivation to apply this technique on other nerve guides (see column 4, last paragraph.) A rejection in view of Li is provided above.

Arguments to claim 39 are moot since the claim has been cancelled and a new grounds of rejection were issued to the claim incorporating the cancelled subject matter.

Regarding claims 40-46, the question of whether or not it would be obvious to combine the Peulve device with the Leong device are moot in view of the new grounds of rejection. The applicant did point out (in the arguments of claim 43) the different method of applying the Neuman method vs. the Peulve method (actually the applicant just repeated what the examiner pointed out in the rejection). Yes, the Stone method utilizes direct injection and the Peulve method utilizes sustained drug delivery. A gene delivery system can be applied in a variety of ways. It is within the skill of one of ordinary skill in the art to take one genetic delivery polymer disclosed in one method and use it in a different method, so long as the purpose of using the polymer remains same. Both Stone and Puelve use the genetic delivery systems to delivery genetic information to spinal cord cells.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A Roberts whose telephone number is (703) 305-7558. The examiner can normally be reached on 7:30-4:00.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3590 for regular communications and (703) 305-3590 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0858.

Paul Roberts
Paul.Roberts@uspto.gov
05/17/04

DAVID O. REIP
PRIMARY EXAMINER
5/18/04